

A Prospective Randomized Placebo-Controlled Multicenter Study on the Efficacy of Intravesical Hyaluronan in Bladder Pain Syndrome/Interstitial Cystitis and Considerations for Designing Future Trials

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ABSTRACT

Background/Objective: Intravesical Glycosaminoglycane (GAG) substitution is widely performed for treatment of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) despite the lack of large controlled trials. Thus, a prospective randomized placebo-controlled trial was performed to assess the efficacy of intravesical hyaluronan therapy in BPS/IC.

Design, Setting, and Participants: 137 patients in 14 urologic clinics in Europe and Canada were enrolled in the study.

Intervention: Eight weekly instillations of a 40 mg hyaluronan solution in Phosphate-Buffered Saline (PBS) were administered in the active treatment group vs. instillation of PBS alone in the control group.

Outcome Measurements and Statistical Analysis: The primary efficacy endpoint was defined as percent responders at week 9 (one week after the last instillation) as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale. Secondary efficacy endpoints addressed pain and urgency scores, voiding frequencies and volumes, the O'Leary-Sant Score and PGA 13 and 17. Statistical evaluation was performed by Student's t-test and by chi square tests.

Results and Limitations: PGA response rates accounted for 61 % in the hyaluronan group, but for a surprising 80 % in the control group. Despite this high response rate in the control group, the intake of concomitant medications aimed at diminishing pelvic pain was about 50% higher in the control vs. the hyaluronan group, which might have influenced reported results. Overall, hyaluronan group patients had a lower chance to need additional symptom-relieving medications compared to placebo therapy. The response rate in the control group deteriorated rapidly upon completion of the study in comparison to the active medication cohort.

Conclusions: While a 61 % symptom improvement rate for intravesical hyaluronan was found in the CISTIC study, superiority over placebo was not demonstrated. Lessons from this first controlled randomized study on hyaluronan, particularly the unequal distribution of concomitant medications, would be helpful in designing future therapeutic trials on BPS/IC.

Introduction

Hyaluronan, the biologic form of hyaluronic acid, is found in numerous tissues in the human body. It is part of the interstitial fluid in connective tissues, but also an important contributor to surface barriers. The importance of hyaluronan as the predominant substance of the Glycosaminoglycan (GAG) layer that protects the urothelial surface of the urinary bladder has been well investigated and documented [1-3].

The impact of a GAG layer defect in Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC), a chronic bladder disease characterized by bladder pain and a variety of voiding symptoms [4,5], was recognized about two decades ago, and the benefit of GAG substitution therapy has been documented in several studies [6-8]. Substantial symptom remission rates have been reported for intravesical hyaluronan instillations by various investigators [9-12]. However, criticism on the concept of GAG deficiency as origin and substitution as therapy of BPS/IC has evolved simultaneously with the publications cited above. One principal argument was that efficacy of intravesical GAG substitution therapies has never been proven in a controlled study [13].

Based on several uncontrolled studies that had shown symptom remission rates between 60 and 85% [9-12], a prospective randomized placebo-controlled double-blind multicenter study (CISTIC) has been set up to evaluate the efficacy of intravesical hyaluronan in women suffering from BPS/IC.

Materials and Methods

Between 2003 and 2007, 130 women with BPS/IC according to ESSIC criteria were enrolled into the CISTIC study. Patients were randomized (by an algorithm disclosed by the central study center after enrolment) to hyaluronan or placebo instillations in a 3:1 ratio to minimize the number of placebo treatments and increase adherence to the protocol.

The study protocol was approved by local ethic boards at all study sites (listed in Table 1).

Inclusion and exclusion criteria are shown in table 2. Based on our experience, all study patients had to have a positive modified potassium test, as described by

Daha et al. [14] Bladder cancer was ruled out by cystoscopy and, if applicable, cytology prior to study entry.

After enrolment in the study, patients received a total of eight weekly instillations of 40 mg hyaluronan in 50 ml phosphate buffered saline (PBS, pH 6.8 to 7.5), or 50 ml PBS alone as a placebo-control. Patients rated bladder pain and voiding symptoms at study initiation and on instillation days, and filled out the O'Leary-Sant-Score [15-17] at entrance and study endpoints. A voiding diary was completed on 3 days per week throughout the treatment period.

Patients received single antibiotic prophylaxis on instillation days to prevent infection by catheterism. Hydrophilic 12 F catheters were used for instillations. Instillation times of two hours were recommended to secure adequate contact times of hyaluronan to urothelium.

Additional medication use in case of bladder symptoms according to the local standard of practice was allowed, every increase of established or addition of new medication was recorded. Similarly, all adverse events occurring throughout the study period, were recorded.

The primary efficacy endpoint was defined as percent responders to treatment at week 9 (one week after the last instillation) as indicated by improvement on a seven-point Patient Global Assessment (PGA) scale: markedly improved – moderately improved – slightly improved – no change – slightly worse – moderately worse – markedly worse.

Patients were further followed for another 8 weeks without instillation therapy up to week 17. The treatment and follow-up schedule is shown in Figure 1.

Secondary efficacy endpoints were: Improvement of BPS/IC symptoms assessed by pain and urgency scores (on a visual analogue scale = VAS rating 0-10), voiding frequencies and volumes (from patient diaries) and on-site questionnaires from week 1 to 9 (weekly) and at week 13 and 17, change in O'Leary-Sant Score at week 1, 9 and 17, and change in PGA at week 5, 13 and 17. Statistical evaluation was performed by Student's t-test for independent and dependent samples, analysis of variance techniques and by chi square tests in r by c

contingency tables. P-values < 0.05 were considered statistically significant.

Table 1: Study Centers.

Center	Number of Recruited Patients
Hôpital Tenon (France)	42 patients
Kingston General Hospital / Queen's University (Canada)	14 patients
Landeskrankenhaus Thermenregion Baden (Austria)	14 patients
University of Münster (Germany)	12 patients
Bestgate Medical Centre (Canada)	12 patients
NsP Zilina (Slovakia)	8 patients
The Male Health Center Toronto (Canada)	6 patients
Adult and Pediatric Urology Center (Canada)	7 patients
Mid Cheshire Hospitals (UK)	5 patients
Kantonsspital Frauenklinik (Switzerland)	5 patients
JLF UK Martin (Slovakia)	5 patients
Hôpital Civil Strasbourg (France)	3 patients
Guelph Urology Center (Canada)	3 patients
Herlev Hospital (Denemark)	1 patient

Total: 137 patients; Evaluable: 130 patients

Results

With 130 evaluable patients, 100 randomized to hyaluronan therapy and 30 to control group, the study actually achieved a 3.3:1 ratio. Patients with complete data sets were included in the final statistical analysis: 95 and 92 patients in the hyaluronan group at week 9 / 17 and all 30 patients in the control group.

The anticipated objectives of the primary study endpoint were clearly failed. Overall symptom improvement rates assessed by PGA Scores (including all categories of improvement) counted for 61 % in the hyaluronan (15 markedly/ 18 moderatley / 28% slightly improved) and 80 % (27/23/30%) in the control group (Table 2, Figure 2). Secondary endpoint analysis gave the following additional results (all summarized in Table 3):

- Assessment at week 17 (after 8 weeks without therapy), showed that symptom improvement was not maintained in the control group and declined to 50%, while hyaluronan patients stayed rather stable (51%) – Figure 2.

Table 2: Inclusion and Exclusion Criteria for CISTIC Study.

Inclusion Criteria
• Female patient with clinical diagnosis of bladder pain syndrome/interstitial cystitis
• Negative blood test for pregnancy at baseline or assurance of state rendering conception impossible
• Sterile bacterial urine culture no more than thirty (30) days prior to first treatment
• An average urinary frequency of at least 11 times per 24-hour day
• An average pain/discomfort score of 4 or greater on a 0-10cm VAS scale
• A reduction of maximal bladder capacity greater than 30% when instilled with 0.2M KCl solution compared to bladder instillation with saline
Exclusion Criteria
• Currently receiving or having had prior therapy with intravesical hyaluronan
• Receiving therapy for less than three months with pentosanpolysulfate, antidepressants, antihistaminics, hormonal agonists or antagonists
• Previously confirmed Hunner’s ulcer
• Bladder capacity > 500 ml on awake cystometry
• Neurologic disease or previous surgery having affected bladder function
• Current diagnosis of chemical, tuberculous or radiation cystitis
• History of bladder or lower ureteral calculi
• History of cancer within the last five years other than adequately treated non-melanoma skin cancers
• Active sexual transmitted disease
• Endometriosis
• Urethral stenosis < 18F

- Symptom deterioration was significantly more frequent in the control (26%) vs. the hyaluronan group (13%) at week 17.
- While there was no statistically significant difference found in frequency/urgency/nocturia for both treatment groups, improvement of pain scores at week 17 was significantly better for hyaluronan patients.
- The only severe adverse event was hospitalization consequent to worsening of bladder pain in one patient from the hyaluronan group.

The most surprising and paradox finding was, that, despite the fact that control group patients indicated a higher rate of symptom improvement, the intake of concomitant medications aimed at diminishing pelvic pain/discomfort was about 50% higher in the control group than in the hyaluronan group (Figure 3,4). In addition, the reported rate of adverse events that also comprised symptoms typical for BPS/IC was about 50 % higher in the control group.

This difference in concomitant medication use uncovered a fact that was unforeseen in the original study design: the RCT (randomized controlled trial) concept of equal comedication between the two study groups was difficult to maintain. Almost all patients (96/100 in the hyaluronan and 27/30 in the control group) took concomitant medications, of which all (analgesics, antidepressants, anticholinergics, hormones, benzodiazepines, corticosteroids, antiallergics, even pentosanpolysulfate) have been used for BPS/IC therapy and might have influenced bladder symptoms. The distribution of medications, however, differed significantly between both patients groups: concomitant use of analgesics was recorded in 37 % of the hyaluronan and 56% of the control group, intake of antidepressants in 16% vs.30%, and of anticholinergics in 9% vs. 15 %.

While symptom improvement at the primary endpoint week 9 was comparable for hyaluronan and control groups, there were significantly more patients showing marked symptom deterioration in the control group ($p < 0.05$). Thus, the probability that patients were performing better with hyaluronan therapy, i.e. that they had a decreased risk for worsening and need of

concomitant BPS/IC specific medication, was significantly higher than for control patients.

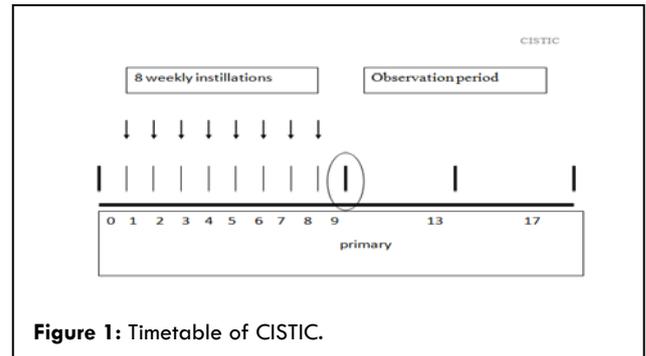


Figure 1: Timetable of CISTIC.

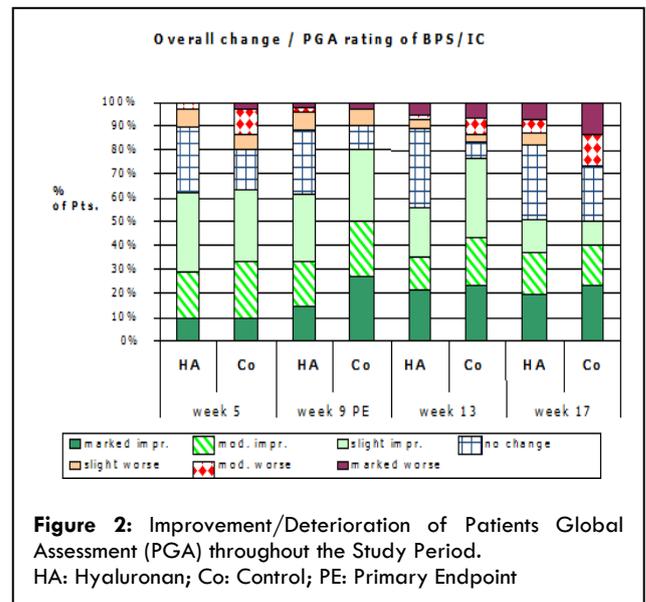


Figure 2: Improvement/Deterioration of Patients Global Assessment (PGA) throughout the Study Period. HA: Hyaluronan; Co: Control; PE: Primary Endpoint

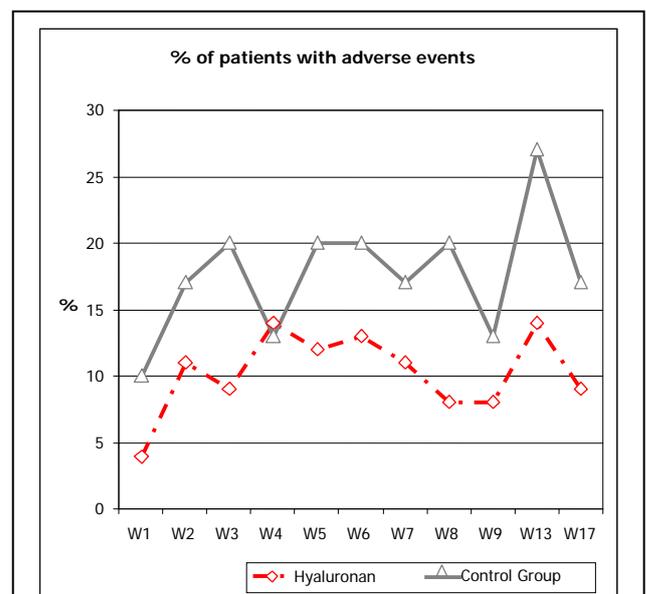


Figure 3: Percentage of patients reporting adverse events throughout the study period.

Table 3: Patient randomization groups – Results.

	Hyaluronan Therapy	Control Group
Total No. of randomized pts.	100	30
Per Protocol Analysis at Week 9 / 17	95/92	30
Median Duration of Bladder Symptoms (Range)	2296 days / 6.3 years (205-14548 days)	1423 days / 3.9 years (194-6482 days)
Median Duration since BPS/IC Diagnosis	646 days / 1.8 years	419 days / 1.2 years
No. of Patients with prior therapy for BPS/IC	72%	63%
Primary endpoint Improvement in Patient Global Assessment (PGA) at Week 9	61 %	80 %
Secondary Endpoint PGA Improvement Week 17	51 %	50 %
Symptom Deterioration W 9	4 %	3 %
Symptom Deterioration W 17	13 %	26 %
Pain Visual Analog Scale (VAS, 0-10) Mean Value Week 0	6.1	5.0
Pain VAS Week 9	4.5	4.5
Pain VAS Week 17	4.0	4.0
Reduction Pain Week 0-17	- 2.1	- 1.0
Urgency VAS Mean Value Week 0	6.7	5.7
UrgencyVAS Week 9	5.1	4.4
Urgency VAS Week 17	4.7	4.4
Reduction Urgency Week 0-17	- 2.0	- 1.3
No. Voids Week 0	19	17
No. Voids Week 9	16	14
No. Voids Week 17	16	15

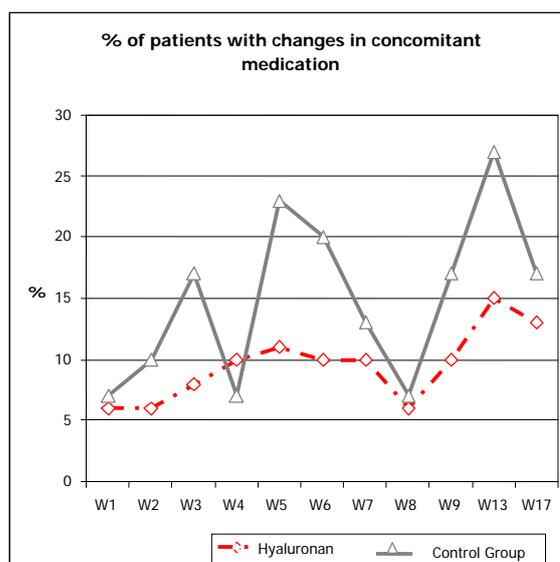


Figure 4: Percentage of Patients with a change of concomitant medications: while at beginning of the study concomitant medication use was comparable for both groups, significant more concomitant medications were used in the control group throughout the study.

Discussion

The results of the CISTIC study bring to the forefront a variety of relevant issues which are idiosyncratic of BPS/IC. A thorough reading and understanding of the study analysis will improve insight into the complexity of trials in BPS/IC and the performance of future studies.

1) The results of the hyaluronan-treated group exactly met the expectations on which CISTIC was statistically based on and conformed to all hitherto published results: The 61 % symptom improvement rate after 8 weekly instillations of hyaluronan was in the range of the pre-study assumptions (50 to 70%) that were based on uncontrolled studies with reported response rates between 65 and 85 % [9-12]. It has to be emphasized that the 61 % improvement rate for hyaluronan is appreciably higher than response rates for other GAG substitutes from controlled studies: 32% with oral Pentosanpolysulfate (Parsons 1993) [18], 40% with intravesical Pentosanpolysulfate (Bade 1997) [19], 39.4% with intravesical Chondroitin Sulphate (Nickel 2010) [20]. However, outcome analysis, especially for older studies, may differ from the criteria used for CISTIC.

2) A placebo response rate of 80% is simply unrealistic. Placebo response rates reported in the relevant medical literature normally lie between 30 and 50 % [16]. Thus, the observed 80 % placebo response rate in CISTIC is definitely outside the 95 % confidence interval that was assumed within limits from 15 to 50 % in the pre-study statistical analysis plan. The possibility of a beneficial effect of repeated PBS instillations on BPS/IC symptoms was considered. There is only one scientific paper that refers to PBS instillations in BPS/IC where the authors did not find any benefit from a single 30 minutes PBS instillation [17], which basically contrasts the surprising results of weekly PBS instillations of about 2 hours duration as in the CISTIC study. However, analysis of concomitant medications uncovered the unequal administration of additional symptom relieving drugs as responsible for the excellent results of the control group.

3) Correction of study results by approved statistical methods was performed to eliminate the influence of concomitant medications that were taken in abundance by control group patients despite the fact that they reported significant symptom improvement. It is assumed that persisting symptoms, unaffected by placebo instillation, prompted control group patients to take symptom-relieving drugs, thus improving their condition. Even if this re-analysis was not planned in the original study design it helped understand the puzzling results. Effect of Concomitant Medication (ECM) analysis states that study patients had an overall benefit from hyaluronan administration compared to placebo. For future studies it would be beneficial to define a (analgesic) rescue medication that can be taken in case of symptom deterioration. This would prevent intake of unmonitored pharmacologically active substances.

4) Although the initial response rate in the control group was high, this effect was not maintained: at week 17, that means 8 weeks after the last instillation, symptom improvement was reported by only 50 %, compared to 51 % in the hyaluronan group. This means an absolute response rate deterioration of 38 % in the control vs. 15 % in the hyaluronan group compared to week 9 scores. If alkalization of the acidic urine to

physiologic values by the PBS buffer solution (which anyway is also part of the hyaluronan preparation) has relieved symptoms exclusively throughout the instillation period (no literature exists to support this assumption), this effect was not maintained, whereas hyaluronan might have restored a urothelial damage or dysfunction with a more permanent effect. Unfortunately, the design of the CISTIC study did not allow further follow-up to assess the further course of disease. From a present point of view the study and follow-up period may have been scheduled too short. Nickel stated that this was one of the main mistakes in studies on pelvic organ pain syndromes [21].

5) The roughly 50 % higher rate of adverse events in the control group may reflect less efficacy of placebo therapy, or side effects of either concomitant medications or, not to forget, grey medication, possibly with OTC (prescription-free/over-the-counter) products, which is a well-recognized core problem in GCP (good clinical practice) trials with placebo – it is neither auditable nor under sponsor or investigator control.

6) Statistical evaluation also detected some unbalanced factors between patients groups: hyaluronan patients showed a higher initial pain score in all assessment tools (O'Leary-Sant Score, VAS, diaries). The average pain score for these patients on VAS was 6.1 vs. 5.0 in the control group. Duration of disease was about 50 % longer in hyaluronan vs. control patients (first bladder symptoms: median 6.3 vs. 3.9 years, diagnosis of BPS/IC median 1.8 vs. 1.2 years). Prior therapies for BPS/IC had been recorded in 72% of the hyaluronan and 63% of the control group. Hyaluronan patients had an average 3.4 therapies before enrolment into the study, compared to 3 in control patients. All these data lead to the conclusion that patients in the hyaluronan group had more severe/advanced disease than control patients.

7) Apart from concomitant medications, patients with more pronounced symptoms, i.e. with an initial VAS pain score > 7 or with a longer course of disease (> 5 years) responded better to hyaluronan vs. placebo (45 vs. 41 % and 52 vs. 43 % at week 17), while symptom deterioration was significantly more frequent in the

control group (20 vs. 41% and 20 vs. 43% at week 17). In other terms: patients with more advanced disease showed a better response to hyaluronan therapy, and symptom deterioration was found in > 40 % in controls at week 17 but only in 20 % of the active treatment group!

8) The unbalanced random assignment has been heavily debated. The 3:1 randomization design had to be selected because in 2003 hyaluronan was freely available as a registered product and reimbursed in some study countries, and patients participation in the study would have been very improbable in case of a 50% chance for placebo treatment. There is a broad statistical literature available that this random procedure has undesirable implications on the statistical power and the precision of the relevant estimates from the data [22]. The slightly lower than expected number of control group patients (30 instead of 33) by itself harbours an about 10% possible deviation of results of the control group

Again, Nickel's experience with studies on pelvic organ pain syndromes 21 has to be emphasized: most of these studies tend to be run too shortly, fail their primary endpoints and fulfill most of the secondary endpoints. This statement as well as the lessons learned from the CISTIC study should be the base for all future controlled studies on BPS/IC therapies. Only optimized study settings and designs will shed light on the value of abundant BPS/IC therapies that are listed in present textbooks and help urologists and patients to define the best treatment strategy for their disease.

Conclusions

Although the expected 61 % symptom improvement rate for hyaluronan instillation therapy was confirmed in the present randomized multicenter trial, superiority of the investigated drug over placebo could not be demonstrated in the original data analysis, as in many other BPS/IC studies. However, the extensively unequal distribution of concomitant medications asked for an adjustment of the results with respect to the use of additional symptom relieving drugs. This additional analysis suggests that the probability that patients were

performing better with hyaluronan therapy and not needing any concomitant medications was significantly higher than with placebo. Lessons learned from this study should be taken into account for future research projects in this condition.

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